CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-827**

STATISTICAL REVIEW(S)

MAR 12 1998

Statistical Review and Evaluation

NDA/ Drug Class:	20-827 / 3S
Applicant:	Advanced Care Products 691 Highway 1, PO Box 6024 North Brunswick, NJ 08902-0724
Name of Drug:	MONISTAT® 3 Vaginal Cream (miconazole nitrate 4%)
Documents Reviewed:	NDA Index and Summary sections (Vol. 1.1) and Statistical sections (Vols. 1.11-1.19) dated March 31, 1997, and diskettes containing SAS datasets provided by the sponsor.
Type of Report:	Statistical Review
Indication:	Treatment of vaginal yeast infections (candidiasis)
Medical Reviewer:	Dr. Dan Davis (HFD-590)

I. Introduction

Miconazole nitrate has been available in several vaginal formulations for the treatment of vulvovaginal candidiasis for 20 years. The currently marketed MONISTAT® Vaginal Cream (miconazole nitrate 2%) delivers 100 mg of miconazole nitrate daily for seven days. A three day treatment is available with MONISTAT® 3 Vaginal Suppositories which contain 200 mg of miconazole nitrate per suppository. Clinical studies previously submitted have shown that seven and three day regimens have similar efficacy and safety profiles. It has been claimed that the consumer preference of treatment is a cream formulation. Therefore, a three day course of treatment with miconazole nitrate 4% vaginal cream containing 200 mg per dose was developed. The purpose of the clinical program for miconazole nitrate 4% vaginal cream was to demonstrate therapeutic equivalence to a reference standard seven day therapy.

Two pivotal Phase III studies were conducted. Both studies were double-blind, randomized, controlled, parallel group, comparative, multicenter studies of patients with documented vulvovaginal candidiasis. Protocol 95-005 compared three days of miconazole nitrate 4% vaginal cream administration to seven days administration of currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream. Protocol 95-007 compared both three days of miconazole nitrate 4% vaginal cream and a five day administration of currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream to the seven day administration of currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream. Only the results of the miconazole nitrate 4%

vaginal cream compared to the currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream are reported for this application. For the purpose of this submission, the objective of these Phase III studies was to determine the efficacy and safety of miconazole nitrate 4% vaginal cream administered for three days compared to the efficacy and safety of currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream administered for seven days in the treatment of women with vulvovaginal candidiasis.

Subjects were enrolled at one of 49 investigative centers as outpatients and treatment was self-administered over seven days. Forty six of 49 investigative centers were in the United States. The remaining three centers were in Latin America. All patients were required to have clinical and microbiological confirmation of disease. Clinical confirmation required the presence of at least one of the following signs and symptoms: vulvovaginal itching, vulvovaginal burning/irritation, vulvar erythema, vulvar edema, vulvar excoriation, vaginal erythema, and vaginal edema. Microbiological confirmation of vulvovaginal candidiasis required documentation of *Candida* species by both 10% KOH preparation and by culture. Patients were seen and evaluated at admission, at Return Visit 1 (8-10 days post-treatment), and at Return Visit 2 (30-35 days post treatment).

The primary efficacy variable was the overall therapeutic cure rate. The overall clinical and microbiological cure rates, cure rates at Return Visits 1 and 2, relapse rates and symptomatic relief were secondary efficacy parameters. A patient was considered a therapeutic cure at Return Visit 1 or 2 if she was both a microbiological cure and a clinical cure at that visit. A clinical cure was based on the improvement in vulvovaginal signs and symptoms of candidiasis which depended on the baseline severity of disease. A microbiological cure required both a negative 10% KOH and a negative BiGGY culture.

II. Efficacy Evaluation

For this review, the key primary efficacy variable for assessing the equivalence of miconazole nitrate 4% vaginal cream and the currently marketed MONISTAT® 7 (miconazole nitrate 2%) Vaginal Cream is the overall therapeutic cure rate. For completeness, overall clinical and microbiological cure rates are also reported. The Cochran-Mantel-Haenszel (CMH) statistic, stratified by investigator, is used to compare the two treatments for overall therapeutic cure rate. Confidence intervals based on the normal approximation of the binomial are used to assess the equivalence of the two treatment groups.

Study 95-005

- Patient Demographics

Study 95-005 had 138 patients randomized to the miconazole nitrate 4% group (M3C) and 142 patients randomized to the MONISTAT® 7 group (M7C). The following

table contains the demographic characteristics by treatment group for all randomized patients. As can be seen from Table 1, distributions of these variables are similar across the two treatment groups ($p > .53$). The descriptive variables race (white versus others) and baseline severity are evaluated using the Cochran-Mantel-Haenszel statistic stratified by investigator. Age was evaluated using ANOVA with investigator effects.

Table 1
Patient Demographics
All Randomized Patients
Study 95-005

		M3C	M7C	P-value
# Patients		138	142	
Age mean (SD)		36.4 (12.2)	35.8 (13.2)	.702
min, max		17, 74	17, 77	
Race (N)	Caucasian	99	96	.531
	Black	22	20	
	Asian	3	4	
	Hispanic	12	20	
	Amer-Indian	1	1	
	Other	1	1	
Baseline Severity (N)				.609
Very Mild		2	3	
Mild		78	83	
Moderate		47	46	
Severe		11	10	

- Analysis Results

The results based on both the sponsor's defined efficacy evaluable and the medical officer's efficacy evaluable are summarized below. The sponsor defined 87 patients in the miconazole nitrate 4% group and 88 patients in the MONISTAT® 7 group as evaluable for overall efficacy. The main reasons for excluding patients from the analysis were negative or missing admission KOH or BiGGY culture, did not return for visits 1 and/or 2, and use of prohibitive medicine. Fourteen of the 17 centers contributed patients to the overall efficacy evaluable dataset.

Table 2 contains the overall clinical, microbiological, and therapeutic cure rates. These rates are all higher for the miconazole nitrate 4% group. However, there is not a statistically significant difference between treatment groups ($p=0.422$) in the overall therapeutic cure rate.

Table 2
Overall Clinical, Microbiological, and Therapeutic Cure Rates
Sponsor's Efficacy Evaluable
Study 95-005

Type of Cure n(%)	M3C N=87	M7C N=88	P-value
Clinical	67 (77.0%)	61 (69.3%)	.574
Microbiological	63 (72.4%)	57 (64.8%)	.699
Therapeutic	58 (66.7%)	52 (59.1%)	.422

The point estimate of the difference between the two treatment groups for the overall clinical, microbiological, and therapeutic cure rates and the corresponding 95% confidence interval are summarized in Table 3. Two 95% confidence intervals are reported in Table 3; the first is the sponsor calculated confidence interval which does not include the correction factor and the second is the confidence interval which uses the continuity correction factor. Since the lower limit of the confidence intervals lies within the lower bound of -20.0% and the confidence interval contains zero, miconazole nitrate 4% vaginal cream is therapeutically equivalent to the currently marketed MONISTAT® 7. This statement also holds for clinical and microbiological equivalence.

Table 3
Difference in Overall Clinical, Microbiological, and Therapeutic Cure Rates
and Corresponding 95% Confidence Intervals
Sponsor's Efficacy Evaluable
Study 95-005

Type of Cure	Difference in Cure Rate (M3C-M7C)	Sponsor's 95% CI	Corrected 95% CI
Clinical	7.7%	(-5.39%, 20.77%)	(-6.52%, 21.92%)
Microbiological	7.6%	(-6.07%, 21.35%)	(-7.25%, 22.45%)
Therapeutic	7.6%	(-6.69%, 21.85%)	(-7.81%, 23.01%)

The medical officer defined 65 patients in the miconazole nitrate 4% group and 79 patients in the MONISTAT® 7 group as evaluable for overall efficacy. The medical officer considered more patients to be non-evaluable than the sponsor. A majority of the additional non-evaluable patients that the medical officer defined are due to return visit window violations. The medical officer enforced the following treatment windows: return visit 1- 7 to 11 days post-treatment and return visit 2- 28 to 37 days post-treatment. These return visit windows are slightly wider than those stated by the sponsor. If window violators are not excluded from the evaluable dataset, 78 patients in the miconazole nitrate 4% group and 85 patients in the MONISTAT® 7 group are evaluable for overall efficacy as defined by the medical officer.

Table 4 contains the overall therapeutic cure rates for the medical officer's evaluable data excluding and including the window violators. Also included in the table is the 95% confidence interval about the difference of the cure rates. Since the lower

limit of the confidence interval lies within the lower bound of -20.0% and the confidence interval contains zero, miconazole nitrate 4% is therapeutically equivalent to the currently marketed MONISTAT® 7. When the windows violators are excluded, these values need to be interpreted with caution since with the reduced sample size, statistical power may no longer be adequate.

Table 4
Overall Therapeutic Cure Rates
Medical Officer's Efficacy Evaluable
Study 95-005

	M3C	M7C	95% CI (M3C- M7C)
Excluding window violators	45/65 (69.2%)	49/79 (62.0%)	(-9.7%, 24.1%)
Including window violators	58/78 (74.4%)	55/85 (64.7%)	(-5.6%, 25.0%)

Study 95-007

- Patient Demographics

Study 95-007 had 142 patients randomized to the miconazole nitrate 4% group (M3C) and 142 patients randomized to the MONISTAT® 7 group (M7C). The following table contains the demographic characteristics by treatment group for all randomized patients. As can be seen from Table 5, distributions of these variables are similar across the two treatment groups ($p > .22$). The descriptive variables race (white versus others) and baseline severity are evaluated using the Cochran-Mantel-Haenszel statistic stratified by investigator. Age was evaluated using ANOVA with investigator effects.

Table 5
Patient Demographics
All Randomized Patients
Study 95-007

		M3C	M7C	P-value
# Patients		142	142	
Age mean (SD)		34.4 (12.3)	32.7 (12.6)	.229
min, max		18, 69	18, 80	
Race (N)	Caucasian	85	81	.451
	Black	26	27	
	Asian	3	3	
	Hispanic	26	25	
	Amer-Indian	1	0	
	Other	1	6	
Baseline Severity (N)				.515
	Very Mild	4	5	
	Mild	76	78	
	Moderate	53	44	
	Severe	9	15	

- Analysis Results

The results based on both the sponsor's defined efficacy evaluable and the medical officer's efficacy evaluable are summarized below. The sponsor defined 98 patients in the miconazole nitrate 4% group and 100 patients in the MONISTAT® 7 group as evaluable for overall efficacy. The main reasons for excluding patients from the analysis were negative or missing admission KOH or BiGGY culture, use of prohibited medication, and delayed or improper use of study medication. Twenty-three of the 32 centers contributed patients to the overall efficacy evaluable dataset.

Table 6 contains the overall clinical, microbiological, and therapeutic cure rates. These rates are all higher for the MONISTAT® 7 group. However, there is not a statistically significant difference between treatment groups (p=0.478) in the overall therapeutic cure rate.

Table 6
Overall Clinical, Microbiological, and Therapeutic Cure Rates
Sponsor's Efficacy Evaluable
Study 95-007

Type of Cure n(%)	M3C N=98	M7C N=100	P-value
Clinical	65 (66.3%)	70 (70.0%)	.574
Microbiological	61 (62.2%)	66 (66.0%)	.699
Therapeutic	57 (58.2%)	62 (63.0%)	.478

The point estimate of the difference between the two treatment groups for the overall clinical, microbiological, and therapeutic cure rates and the corresponding 95% confidence interval are summarized in Table 7. Two 95% confidence intervals are reported in table 6; the first is the sponsor calculated confidence interval which does not include the correction factor and the second is the confidence interval which uses the continuity correction factor. Since the lower limit of the confidence intervals lies within the lower bound of -20.0% and the confidence interval contains zero, miconazole nitrate 4% vaginal cream is therapeutically equivalent to the currently marketed MONISTAT® 7. This statement also holds for clinical and microbiological equivalence.

Table 7
Difference in Overall Clinical, Microbiological, and Therapeutic Cure Rates and Corresponding 95% Confidence Intervals
Sponsor's Efficacy Evaluable
Study 95-007

Type of Cure	Difference in Cure Rate (M3C-M7C)	Sponsor's 95% CI	Corrected 95% CI
Clinical	-3.7%	(-16.64%, 9.30%)	(-17.68%, 10.28%)
Microbiological	-3.8%	(-17.11%, 9.59%)	(-18.17%, 10.57%)
Therapeutic	-4.8%	(-18.44%, 8.76%)	(-19.41%, 9.81%)

Since this study was originally designed with a third treatment arm, a 5 day treatment, it is conceivable that multiple comparisons of the Monistat® 7 group were performed. Even though the results of that treatment arm are not presented in this submission, an adjustment for the family of tests which may be performed should be made. For this review, an adjustment to alpha was made using [redacted] assuming two multiple comparisons. Therefore, in addition to the 95% confidence interval reported in Table 7, a 97.3% (α=.027) confidence interval for the difference in therapeutic cure rates was calculated. The confidence interval which adjusts for multiple comparisons is (-21.4%, 11.8%).

Reviewer's Comment: It should be noted that by adjusting for multiple comparisons, the lower limit of the confidence interval no longer lies within the lower bound of -20% to claim therapeutic equivalence. It is a clinical judgment as to whether this is of clinical importance since the analysis of the medical officer efficacy evaluable data does not lead to this conclusion (see Table 8).

The medical officer defined 78 patients in the miconazole nitrate 4% group and 84 patients in the MONISTAT® 7 group as evaluable for overall efficacy. More patients were considered to be non-evaluable by the medical officer than the sponsor. Almost half of the medical officer defined non-evaluable patients were due to window violations. If window violators are not excluded from the evaluable dataset, 97 patients in the miconazole nitrate 4% group and 99 patients in the MONISTAT® 7 group are evaluable for overall efficacy.

Table 8 contains the overall therapeutic cure rates for the medical officer's evaluable data excluding and including the window violators. The confidence interval about the difference of the cure rates which adjusts alpha for multiple comparisons using [redacted] (see discussion above) is also presented in Table 8. Since the lower limit of the confidence interval lies within the lower bound of -20.0%, miconazole nitrate 4% is therapeutically equivalent to the currently marketed MONISTAT® 7. When the windows violators are excluded, these values need to be interpreted with caution since with the reduced sample size, statistical power may no longer be adequate.

Table 8
Overall Therapeutic Cure Rates
Medical Officer's Efficacy Evaluable
Study 95-007

	M3C	M7C	Adjusted* CI (M3C- M7C)
Excluding window violators	46/78 (59.0%)	49/84 (58.3%)	(-17.7%, 19.1%)
Including window violators	62/97 (63.9%)	64/99 (64.6%)	(-16.9%, 15.4%)

*Adjusted for multiple comparisons, using Dunnett's adjustment to alpha.

Subset Analysis

To investigate differences among demographic subsets, subgroups of patients were formed by race (white vs. others) and age (≤ 45 vs. ≥ 46). Since all subjects are females, a subset analysis by gender is not necessary and the age division was chosen to see if a difference between perimenopausal and postmenopausal females exists. The data defined by the sponsor as valid for overall efficacy in Study 95-005 and Study 95-007 were pooled by this reviewer to provide a larger sample size for this exploratory analysis. For each subset, overall therapeutic cure rates were compared for each treatment group. There are no statistically significant differences in the overall therapeutic cure rates for any subset. Females age 45 or less seem to have higher overall therapeutic cure rates than females 46 and older. White subjects in the miconazole nitrate 4% group have slightly higher overall therapeutic cure rates than do the white subjects in the MONISTAT® 7 group. However, the reverse is true for non-white subjects. Table 9 includes the overall therapeutic cure rates by each subset variable.

Table 9
Overall Therapeutic Cure Rates by Subset
Pooled Studies 95-005 and 95-007

M3C	M7C	P-value	M3C	M7C	P-value
White			Non-White		
(N=117)	(N=117)		(N=68)	(N=71)	
75 (64.1%)	70 (59.8%)	.501	40 (58.8%)	45 (63.4%)	.582
≤ 45			≥ 46		
(N=144)	(N=97)		(N=41)	(N=35)	
93 (64.6%)	97 (63.4%)	.832	22 (53.7%)	18 (51.4%)	.846

III. Safety Evaluation

The following is an analysis of the safety data provided by the sponsor. Since Protocol 95-005 and Protocol 95-007 are similarly designed, the data of the two studies is pooled to allow for larger sample sizes. Table 10 summarizes the reported adverse events in the two studies. The total number of patients valid for safety, the number and percent of patients with at least one reported adverse event, the total number of adverse events reported, and the number and percent of adverse events that were considered possibly, probably, or highly probably related to study drug are included in the table for miconazole nitrate 4% cream and MONISTAT® 7.

Table 10
Adverse Events
Protocols 95-005 and 95-007 Combined

	M3C	M7C
Total # Patients Valid for Safety	274	272
# (%) Patients with AE	179 (65.3%)	178 (65.4%)
Total # AEs Reported	543	586
# (%)Related AE's	229 (42.2%)	204 (34.8%)

Note: Related corresponds to possibly, probably, or highly probably related.

Overall, safety is comparable between the two treatment groups. Adverse events were reported by about two-thirds of women in each treatment group. The MONISTAT® 7 group reported slightly more adverse events than the miconazole nitrate 4% group. However, more of the adverse events reported in the miconazole nitrate 4% group were considered related to study drug than in the MONISTAT® 7 group. The majority of the related adverse events for both groups were pain, irritation, burning, or pruritus of the female genitalia.

Adverse events reported by more than 2% of patients in either treatment group are summarized in Table 11.

Table 11
Adverse Events Reported by > 2% of Patients
Protocols 95-005 and 95-007 Combined

Adverse Event	M3C (N=274)	M7C (N=272)
Pruritus, external female genitalia	69 (25.2%)	67 (24.6%)
Burning, female genitalia	68 (24.8%)	62 (22.8%)
Headache	50 (18.2%)	53 (19.5%)
Irritation, female genitalia	51 (18.6%)	52 (19.1%)
Discharge, female genitalia	10 (3.6%)	17 (6.3%)
Nausea	6 (2.2%)	12 (4.8%)
Congestion, respiratory	7 (2.6%)	12 (4.8%)
Dysmenorrhea	13 (4.7%)	12 (4.4%)
Upper Respiratory Infection	7 (2.6%)	11 (4.0%)
Cramps, GI	10 (3.6%)	9 (3.3%)
Pain, abdominal	9 (3.3%)	6 (2.2%)
Diarrhea	5 (1.8%)	9 (3.3%)
Pain, female genitalia	8 (2.9%)	2 (0.7%)
Erythema, female genitalia	4 (1.5%)	8 (2.9%)
Pharyngitis	6 (2.2%)	7 (2.6%)
Pain, trunk	6 (2.2%)	5 (1.8%)

Reviewer's Conclusions (which may be conveyed to the sponsor in the action letter)

1. *Based on the efficacy analyses performed, miconazole nitrate 4% administered for 3 days has been shown to be therapeutically equivalent to the currently marketed MONISTAT® 7. (Study 95-005 see Table 3 Sponsor's efficacy evaluable and Table 4 Medical Officer's efficacy evaluable. Study 95-007 see Table 7 Sponsor's efficacy evaluable and Table 8 Medical Officer's efficacy evaluable.)*

2. *Overall, safety is comparable between the two treatment groups. Adverse events were reported by about two-thirds of women in each treatment group. The MONISTAT® 7 group reported slightly more adverse events than the miconazole nitrate 4% group. However, more of the adverse events reported in the miconazole nitrate 4% group were considered related to study drug than in the MONISTAT® 7 group. The majority of the related adverse events for both groups were pain, irritation, burning, or pruritus of the female genitalia.*

/S/ 3/12/98
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This review contains 10 pages.

MAR 25 1998

Addendum to Statistical Review dated March 12, 1998

NDA #: 20-827

Applicant: Advanced Care Products

Name of Drug: MONISTAT® 3 Vaginal Cream (miconazole nitrate 4%)

Indication: Treatment of vaginal yeast infections (candidiasis)

This addendum is in response to a request by the reviewing microbiologist. The reviewing microbiologist asked for an analysis of response rates for various fungal species. Table 1 includes the FDA microbiologist's analysis of the microbiologic response for Studies 95-005 and 95-007. Only data for *C. albicans* and *T. glabrata* are reported in the table. Patients were categorized as non-interpretable if there was a positive culture at visit 1, a negative culture at return visit 1, and a positive culture at return visit 2. These results were considered non-interpretable by the reviewing microbiologist because colonization could not be differentiated from relapse. (See microbiologist's review for complete data on all strains).

Table 1
FDA Assessment of Microbiologic Results by Strain

		Study 95-005		Study 95-007	
		Miconazole Nitrate		Miconazole Nitrate	
Strain	Response	4%	2%	4%	2%
C. albicans	Cure	61	60	47	58
	Failure	9	5	10	9
	Non-interpretable	11	6	11	9
T. Glabrata	Cure	0	0	1	1
	Failure	2	4	3	0
	Non-interpretable	0	0	1	1

The data for the two studies was combined in order to assess differences in response within a given strain. This was assessed by the chi-square test. There are no statistically significant differences in the responses for either of the fungal strains in question. The p-values for the chi-square test are: *C. albicans*- p=0.45 and *T. glabrata*- p=0.67. Due to the small cell sizes for *T. glabrata*, the chi-square may not be a valid test. Therefore, Fisher's Exact test was also performed and the result of this test is p=1.0.

Reviewer's Conclusions

There are no statistically significant differences in the microbiological response rates for either C. albicans (chi-square p=0.45) or T. glabrata (Fisher's Exact p=1.0) as determined from the combined data from studies 95-005 and 95-007.

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This review contains 2 pages.